Highlights from Recent Cancer Literature

Angiopoietin-2: An Attractive Target for Improved Antiangiogenic Tumor Therapy
Damien Gerald, Sudhakar Chintharlapalli, Hellmut G. Augustin, and Laura E. Benjamin

Ion Channels and Transporters in Cancer: Pathophysiology, Regulation, and Clinical Potential
Stine F. Pedersen and Christian Stock

G-protein Inactivator RGS6 Mediates Myocardial Cell Apoptosis and Cardiomyopathy Caused By Doxorubicin
Juanqi Yang, Biswanath Maity, Jie Huang, Zhan Gao, Adele Stewart, Robert M. Weiss, Mark E. Anderson, and Rory A. Fisher

Trp53 Inactivation in the Tumor Microenvironment Promotes Tumor Progression by Expanding the Immunosuppressive Lymphoid-like Stromal Network
Gang Guo, Luis Marrero, Paulo Rodriguez, Luis Del Valle, Augusto Ochoa, and Yan Cui

Phase I Trial of Recombinant Modified Vaccinia Ankara Encoding Epstein–Barr Viral Tumor Antigens in Nasopharyngeal Carcinoma Patients

Precis: Vaccination of nasopharyngeal carcinoma patients targeting two pathogenic viral antigens produces potent immune responses after they have completed chemo/radiotherapy.

Earlier Detection of Breast Cancer with Ultrasound Molecular Imaging in a Transgenic Mouse Model
Sanitha V. Bachawal, Kristin C. Jensen, Amelie M. Lutz, Sanjiv S. Gambhir, Francois Tranquart, Lu Tian, and Jürgen K. Willmann

Precis: This study lays the foundation for the development of a novel ultrasound-based imaging approach for earlier detection of breast cancer and paves the way for translational clinical trials in the future.

Collections of Simultaneously Altered Genes as Biomarkers of Cancer Cell Drug Response
David L. Masica and Rachel Karchin

Precis: New methods are offered to improve the identification of drug response biomarkers in cancer cells.

Therapeutic Efficacy of Bifunctional siRNA Combining TGF-β1 Silencing with RIG-I Activation in Pancreatic Cancer
Jonathan Ellermeier, Jiwu Wei, Peter Duewell, Sabine Hoves, Mareike R. Stieg, Tina Adunka, Daniel Noerenberg, Hans-Joachim Anders, Doris Mayr, Hendrik Poeck, Gunther Hartmann, Stefan Endres, and Max Schnurr

Precis: The potency of a therapeutic siRNA can be increased by a parallel strategy to combinatorially activate an RNA helicase that triggers inflammatory responses to double-stranded viral RNA, with implications for understanding how to reprogram the tumor microenvironment to destroy tumor cells.
LOX-Mediated Collagen Crosslinking Is Responsible for Fibrosis-Enhanced Metastasis

Thomas R. Cox, Demelza Bird, Ann-Marie Baker, Holly E. Barker, Melissa W-Y. Ho, Georgina Lang, and Janine T. Erler

Précis: The fibrotic status of a metastatic niche that is determined by the extracellular matrix plays a pivotal role in determining colonization of new sites by circulating tumor cells.

Evidence for a Role of the PD-1:PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma

Sofia Lyford-Pike, Shiwen Peng, Geoffrey D. Young, Janis M. Taube, William H. Westra, Belinda Akpeng, Tullia C. Bruno, Jeremy D. Richmon, Hao Wang, Justin A. Bishop, Lieping Liu, Yutaka Ogawa, Koji Kono, and Dario Campana

Précis: Findings illustrate how to increase the antitumor efficacy of NK cell therapy, a strategy that may be used to fight nearly any kind of human cancer.

MOLECULAR AND CELLULAR PATHOBIOLOGY

Transcription Factor YY1 Contributes to Tumor Growth by Stabilizing Hypoxia Factor HIF-1α in a p53-Independent Manner

Shourong Wu, Vivi Kasim, Mitsunobu R. Kano, Sayaka Tanaka, Shinuike Ohba, Yutaka Mizu, Kanjiro Miyata, Xueying Liu, Ako Matsushita, Ung-il Chung, Li Yang, Kazunori Katoaka, Nobuhiro Nishiyama, and Makoto Miyagishi

Précis: Findings suggest a mechanistic strategy to block a core hypoxia-driven progression pathway regardless of p53 status.

Arkadia Regulates Tumor Metastasis by Modulation of the TGF-β Pathway

Marco A. Briones-Orta, Laurence Levy, Chris D. Madsen, Debipriya Das, Yigit Erker, Erik Sahai, and Caroline S. Hill

Précis: An E3 ubiquitin ligase in the TGF-β signaling pathway is not required to regulate tumor growth but to colonize metastasis sites, suggesting novel antimetastatic strategies.

Phosphorylation of Ribosomal Protein S6 Attenuates DNA Damage and Tumor Suppression during Development of Pancreatic Cancer

Abed Khalaileh, Avigail Dreazen, Areej Khatib, Roy Apel, Avital Swisa, Norma Kidess-Bassir, Anirban Maitra, Oded Meyuhas, Yuval Dor, and Gideon Zamir

Précis: Findings reveal that a key mTOR effector molecule is crucial for initiation of K-Ras-induced pancreatic cancers, illuminating the centrality of this mTOR pathway to evade p53-mediated tumor suppression in this setting.

HLA-Restricted CTL That Are Specific for the Immune Checkpoint Ligand PD-L1 Occur with High Frequency in Cancer Patients

Shamaila Munir, Gitte Holmen Andersen, Özcan Met, Marco Donia, Thomas Mørch Frøsig, Stine Kier Larsen, Tobias Wiernfeldt Klausen, Inge Marie Svane, and Mads Hald Andersen

Précis: PD-L1-specific cytotoxic T cells described for the first time in this study may be useful to harness for cancer immuno therapy to defeat mechanisms of immune escape used in various cancers mediated by the PD1 pathway.
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
<th>Summary</th>
<th>Featured Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>1831</td>
<td>Proliferation-Independent Control of Tumor Glycolysis by PDGFR-Mediated AKT Activation</td>
<td>Cong Ran, Huan Liu, Yasuyuki Hitoshi, and Mark A. Israel</td>
<td>Precise: Findings argue that tyrosine kinase growth factor signaling directly affects glucose metabolism in glioma and is not a secondary response to enhanced proliferation, as suggested in other cancer models.</td>
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<td>1844</td>
<td>Telomere Length and Telomerase Activity Impact the UV Sensitivity Syndrome Xeroderma Pigmentosum C</td>
<td>Gerdine J. Stout and Maria A. Blasco</td>
<td>Precise: Findings reveal a role for the DNA repair protein XPC in telomere stability and how activation occurs for the ALT pathway of telomere maintenance, a broadly important aspect of tumor formation.</td>
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<td>1855</td>
<td>xCT Inhibition Depletes CD44v-Expressing Tumor Cells That Are Resistant to EGFR-Targeted Therapy in Head and Neck Squamous Cell Carcinoma</td>
<td>Momoko Yoshikawa, Kenji Tsuchihashi, Takatsugu Ishimoto, Toshiumi Yae, Takeshi Motohara, Eiji Suqihara, Nobuyuki Onishi, Takashi Masuko, Kunio Yoshibawa, Shuichi Kashawashiri, Makio Mukai, Seiji Asoda, Hiromasa Kawan, Taneki Nakagawa, Hideyuki Saya, and Osamu Nagano</td>
<td>Precise: Cells that express variant isoforms of the stem cell-determining factor CD44 rely on the activity of a cystine transporter subunit that affects redox status and EGFR function.</td>
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<td>1876</td>
<td>MicroRNA-Related Genetic Variants Associated with Clinical Outcomes in Early-Stage Non–Small Cell Lung Cancer Patients</td>
<td>Xia Pu, Jack A. Roth, Michelle A.T. Hildebrandt, Yuqing Ye, Hua Wei, John D. Minna, Scott M. Lippman, and Xifeng Wu</td>
<td>Precise: This large study of non-small cell lung cancer suggests that miRNA-related polymorphisms can predict clinical outcomes at a level that may be superior to other markers developed previously.</td>
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<td>1883</td>
<td>Genetic Variation in Transforming Growth Factor Beta 1 and Mammographic Density in Singapore Chinese Women</td>
<td>Eunjuang Lee, David Van den Berg, Chris Hsu, Giske Ursin, Woon-Puay Koh, Jian-Min Yuan, Daniel O. Stram, Mimi C. Yu, and Anna H. Wu</td>
<td>Precise: Host genetic polymorphisms in a key growth factor in breast cancer may help identify women at an increased risk of breast cancer.</td>
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<td>1892</td>
<td>Focused Ultrasound Delivers Targeted Immune Cells to Metastatic Brain Tumors</td>
<td>Ryan Alkins, Alison Burgess, Milan Ganguly, Giulia Francia, Robert Kerbel, Winfried S. Wels, and Kullervo Hynynen</td>
<td>Precise: Noninvasive MR-guided focused ultrasound allows targeted natural killer cells to circumvent the blood-brain barrier and treat HER2-amplified breast metastasis in the brain.</td>
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<td>1900</td>
<td>Caveolin-1–LRP6 Signaling Module Stimulates Aerobic Glycolysis in Prostate Cancer</td>
<td>Salahaldin A. Tahir, Guang Yang, Alexei Goltslov, Ki-Duk Song, Chengzhun Ren, Jianxiang Wang, Wenjun Chang, and Timothy C. Thompson</td>
<td>Precise: This study offers mechanistic insights into how aerobic glycolysis is increased in prostate cancer, possibly revealing critical targets for effective antimetabolic therapy in this setting.</td>
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1958

Phenotypic Profiling of mTOR Complex 2 Is Involved in Alkaline Phosphatase ALPPL-2 Is a Novel Inhibitor of STAT3 Mixed Lineage Kinase MLK4 Is Activated in Colorectal Cancers Where It Synergistically Cooperates with Activated RAS Signaling in Driving Tumorigenesis

Miriam Martini, Mariangela Russo, Simona Lamba, Elisa Vitelli, Emily Hannah Crowley, Francesco Sassi, Davide Romanelli, Milo Frattini, Antonio Marchetti, and Alberto Bardelli

Precis: Findings support the development of small molecule inhibitors of the kinase MLK4 to treat the significant number of KRAS-mutant colorectal cancers that arise in humans.

1922

A Novel Inhibitor of STAT3 Homodimerization Selectively Suppresses STAT3 Activity and Malignant Transformation

Xiaolei Zhang, Ying Sun, Roberta Pireddu, Hua Yang, Muradi K. Ursan, Harshani R. Lawrence, Wayne C. Guida, Nicholas J. Lawrence, and Said M. Sebti

Precis: STAT3 provides critical support in cancer cells and the immune microenvironment in tumors, but bioactive small molecule inhibitors that offer tractable qualities for clinical translation have been elusive.

1934

Alkaline Phosphatase ALPPL-2 Is a Novel Pancreatic Carcinoma-Associated Protein

Pooja Dua, Hye Suk Kang, Seung-Mo Hong, Ming-Sound Tsao, Soyoun Kim, and Dong-ki Lee

Precis: An aptamer selection strategy identifies an enzyme that may be useful for blood-based detection of pancreatic cancer.

1946

mTOR Complex 2 Is Involved in Regulation of Chl-Dependent c-FLIP Degradation and Sensitivity of TRAIL-Induced Apoptosis

Liqun Zhao, Ping Yue, Fadlo R. Khuri, and Shi-Yong Sun

Precis: Findings show how mTORC2 stabilizes the FLIP apoptotic regulators, thereby connecting mTORC2 signaling to death receptor-mediated apoptosis.

1958

Phenotypic Profiling of DPDY Variations Relevant to 5-Fluourouracil Sensitivity Using Real-time Cellular Analysis and In Vitro Measurement of Enzyme Activity

Steven M. Offer, Natalie J. Wegner, Croix Fossum, Kangsheng Wang, and Robert B. Diasio

Precis: An understanding of the contribution of DPDY alleles to 5-FU toxicity will facilitate the generation of clinically relevant predictive tests and promote the individualization of treatment based on genotype.

1993

Genetic Amplification of the NOTCH Modulator LNX2 Upregulates the WNT/β-Catenin Pathway in Colorectal Cancer

Jordi Camps, Jason J. Pitt, Georg Emons, Amanda B. Hummon, Chanelle M. Case, Mariam Grade, Tamara L. Jones, Quang T. Nguyen, B. Michael Ghadimi, Tim Beisbarth, Michael J. Dillilipantionio, Natasha J. Caplen, and Thomas Ried

Precis: Notch and Wnt signaling pathways are upregulated by overexpression of a ligand for the endocytic adaptor protein Numb, a Notch inhibitory protein, coordinately stimulating both of these critical oncogenic pathways in colorectal cancer.

2003

Precis: Inhibition of PERK kinase, which controls the unfolded protein response (UPR), a near universally elevated process in cancer cells, was also found unexpectedly to affect amino acid metabolism, blood vessel density, and vascular perfusion in tumors.

2004

Characterization of a Novel PERK Kinase Inhibitor with Antitumor and Antiangiogenic Activity

Charity Atkins, Qi Liu, Elisabeth Minthorn, Shu-Yun Zhang, David J. Figueroa, Katherine Moss, Thomas B. Stanley, Brent Sanders, Aaron Goetz, Nathan Gaul, Anthony E. Choudhry, Hasan Alsaid, Beat M. Jucker, Jeffrey M. Axten, and Rakesh Kumar

Precis: Findings of this study suggest a rational new target for anti-EMT therapy of cancer stem cells, perhaps relevant to many types of malignancy.

2006

Involvement of Lyn and the Atypical Kinase SgK269/PEAK1 in a Basal Breast Cancer Signaling Pathway


Precis: This study addresses a rationale to target basal breast cancers, also known as triple negative breast cancers, which present a major clinical challenge due to their aggressive nature and lack of targeted treatments.
ABOUT THE COVER

Inactivation of the tumor suppressor p53 frequently occurs in tumors and tumor-associated stromal cells. This study shows that p53 dysfunction in tumor-associated stroma of B16F1 melanoma favors tumor establishment and progression by promoting an inflammatory microenvironment. Using immunofluorescence, it was found that lymphoid-like fibroblastic reticular cells, which express ER-TR7 (green), GP38 (red), and α-SMA (blue), were markedly expanded in the tumor microenvironment lacking functional p53. The expansion of this specialized stromal network was associated with augmented myeloid derived suppressor cells and angiogenesis. For details, see the article by Guo and colleagues on page 1668.
Cancer Research

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